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PATENT- OG VAREMÆRKESTYRELSEN

Pharmaceutical composition comprising a solid solution of tacrolimus and/or an analogue thereof

Field of the invention

The present invention relates to a solid solution of tacrolimus and/or an analogue thereof for pharmaceutical use. The solid solution contains tacrolimus and/or an analogue thereof dissolved in a solid carrier material that is a polymeric substance that is miscible with water.

The solid solution provided by the present invention presents tacrolimus and/or an analogue thereof in a freely accessible form for absorption into the systemic circulation upon oral or topical administration and is a suitable basic material for designing controlled release pharmaceutical compositions for oral use.

Background of the invention

Tacrolimus is a widely used compound that has immunosuppressive activity, antimicrobial activity and other pharmacological activities and is of value for the treatment or prevention of rejection reactions by transplantation of organs or tissues, graft versus host diseases, autoimmune diseases and infectious diseases.

Absorption of tacrolimus from the gastrointestinal tract after oral administration is rapid with a mean time-to–peak concentration (t_{max}) of approximately 1-2 hours after administration to healthy subjects or kidney or liver transplanted patients, but incomplete and variable. The bioavailability is generally as low as at the most about 20% after oral administration.

Accordingly, there is a need for pharmaceutical compositions with improved properties that results in an increased bioavailability compared to known compositions. The object of the present invention is to provide means for obtaining an improved bioavailability of tacrolimus after oral administration by employing tacrolimus in the form of a solid solution. Furthermore, once tacrolimus is available in a suitable form, i.e. in the form of a solid solution, this may be further processed to other dosage form suitable for oral administration.

For oral administration, tacrolimus is currently formulated and marketed as soft gelatine capsules comprising the equivalent of 0.5, 1 or 5 mg anhydrous tacrolimus and

marketed under the trade name Prograf® and Protropic®. The recommended initial oral dose is from about 0.1 - 0.2 mg/kg/day in patients. The dose aims at a certain trough plasma level from about 5 to about 20 ng/ml. However, tacrolimus normally lead to great variations between peak and trough values, which from therapeutic point of view is desirable to minimize this variation so that the plasma level is more constant.

Accordingly, there is also a need for new pharmaceutical compositions comprising tacrolimus exhibiting, a reproducible, controlled release of the drug with plasma levels which can stay within the narrow therapeutic window (see Fig. 1) for an extended period of time, without loosing significant bioavailability. The present invention provides such compositions, wherein tacrolimus and/or an analogue thereof is present in the composition in the form of a solid solution and the composition further comprises one or more release modifying agents.

Description of the invention

The present invention provide a solid solution for pharmaceutical use comprising tacrolimus and/or an analogue thereof dissolved in a water-miscible solid carrier, wherein the concentration of tacrolimus in the water-miscible carrier is at the most 15% w/w.

The present inventors have found that it is advantageous to use tacrolimus in dissolved form like in a solid solution. By use of tacrolimus in dissolved form it is already in a form that enables a fast release of tacrolimus and thereby enables that tacrolimus is present in a readily absorbable form that makes it possible to improve the bioavailability compared to the known compositions.

The solid solutions are also ideal for topical administration of tacrolimus and/or analogues thereof, as the melted solution easily applies to a "stick". The solid stick is then used for dermal administration.

Within the scope of the present invention tacrolimus may be used in any physical form (crystals, amorphous powder, any possible polymorphs, any possible solvates including the hydrate, anhydrate, complexes thereof etc.). Included is also any analogue, derivative or active metabolite of tacrolimus, pharmaceutically acceptable salts, solvates, complexes and prodrugs thereof.

In the present context, the term "solid solution" means that tacrolimus is present in dissolved form, i.e. in the form of a molecular solution such as a monomolecular distribution of tacrolimus within the solid carrier. In contrast to compositions wherein tacrolimus is present in the form of solid finely divided particles that are suspended in a vehicle, the present inventors have found that in order to ensure a suitable bioavailability it is of importance that tacrolimus is on dissolved form. To this end, the inventors have found that the solid carrier should be present in relatively large excess compared with tacrolimus. Accordingly, in one aspect of the invention, the concentration of tacrolimus in the water-miscible carrier is at the most 10% w/w such as, e.g., at the most 8% w/w, at the most 6% w/w, at the most 5% w/w, at the most 4%w/w, at the most 3% w/w or at the most 2% w/w. The low concentration of tacrolimus in the solid carrier ensures that tacrolimus is dissolved and, furthermore, the solid carrier may aid in releasing tacrolimus in a suitable manner. In order to obtain a suitable amount in the final composition there is a lower limit for the concentration of tacrolimus in the solid solution. Thus, in a further aspect of the invention, the concentration of tacrolimus in the water-miscible carrier is at least about 0.01% w/w such as, e.g., at least about 0.05% w/w, at least about 0.1% w/w, at least about 0.5% w/w or at least about 1% w/w.

As appears from the above, an important ingredient in the solid solution is the water-miscible carrier. In the present context, the term "water-miscible carrier" is intended to denote a carrier that is more hydrophilic than hydrophobic and, accordingly, can be admixed with water and the resulting mixture being a one phase system, at least at certain water/polymer ratios. It should be noted that the use of the term "water-miscible" instead of the term "water-soluble" relates to the fact that it normally is difficult to determine the water solubility of a specific polymer because it may swell upon contact with water and, accordingly, a more correctly applied term is "water-miscible" that is known by a person skilled in the art (a polymer cannot be a polymer, if it is soluble, hence the term "water soluble" polymer do not make sence).

Suitable water-miscible carriers that can be used in the solid solution according to the invention may be selected from the group consisting of polyethylene glycols polyoxyethylene oxides, poloxamers, polyoxyethylene stearates, poly-epsilon caprolactone, polyvinylpyrrolidones, polyvinyl-polyvinylacetate copolymer (PVP-PVA), polyvinyl alcohol (PVA), polymethacrylic polymers (Eudragit RS; Eudragit RL, Eudragit NE, Eudragit E), cellulose derivatives including hydroxypropyl methylcellulose (HPMC),

hydroxypropyl cellulose (HPC), methylcellulose, sodium carboxymethylcellulose, hydroxyethyl cellulose, pectins, cyclodextrins, galactomannan, alginates, xanthan gums, carbohydrates, Gelucire, and mixtures thereof.

The carrier or mixture of carrier must be solid at room temperature, i.e. the melting point of the carrier (if used as the sole carrier) or of the carrier mixture must be at least 20 °C.

In an interesting embodiment, the water-miscible carriers that can be used in the solid solution according to the invention is a polyethylene glycol having an average molecular weight in a range of from about 1,000 to about 35,000 such as, e.g., from about 1,000 to about 35,000 such as, e.g., polyethylene glycol 1,000, polyethylene glycol 2,000, polyethylene glycol 3,000, polyethylene glycol 4,000, polyethylene glycol 5,000, polyethylene glycol 6000, polyethylene glycol 7,000, polyethylene glycol 8,000, polyethylene glycol 9,000 polyethylene glycol 10,000, polyethylene glycol 15,000, polyethylene glycol 20,000, or polyethylene glycol 35,000. In certain situations polyethylene glycol may be employed with a molecular weight from about 35,000 to about 100,000.

In another interesting embodiment, the water-miscible carriers that can be used in the solid solution according to the invention is polyethylene oxide having a molecular weight of from about 2,000 to about 7,000,000 such as, e.g. from about 2,000 to about 100,000, from about 5,000 to about 75,000, from about 10,000 to about 60,000, from about 15,000 to about 50,000, from about 20,000 to about 40,000, from about 100,000 to about 7,000,000 such as, e.g., from about 100,000 to about 1,000,000, from about 100,000 to about 600,000, from about 100,000 to about 400,000 or from about 100,000 to about 300,000.

In another embodiment, the water-miscible carriers that can be used in the solid solution according to the invention is a poloxamer such as, e.g. Poloxamer 188, Poloxamer 237, Poloxamer 338 or Poloxamer 407 or other block copolymers of ethylene oxide and propylene oxide such as the Pluronic® and/or Tetronic® series. Suitable block copolymers of the Pluronic® series include polymers having a molecular weight of about 3,000 or more such as, e.g. from about 4,000 to about 20,000 and/or a viscosity (Brookfield) from about 200 to about 4,000 cps such as, e.g., from about 250 to about 3,000 cps. Suitable examples include Pluronic® F38, P65, P68LF, P75, F77,

P84, P85, F87, F88, F98, P103, P104, P105, F108, P123, F123, F127, 10R8, 17R8, 25R5, 25R8 etc. Suitable block copolymers of the Tetronic® series include polymers having a molecular weight of about 8,000 or more such as, e.g., from about 9,000 to about 35,000 and/or a viscosity (Brookfield) of from about 500 to about 45,000 cps such as, e.g., from about 600 to about 40,000. The viscosities given above are determined at 60 °C for substances that are pastes at room temperature and at 77 °C for substances that are solids at room temperature.

In another embodiment, the water-miscible carrier for use in a solid solution according to the invention is e.g. polyglycolised glycerides including Gelucire 50/13, or other Gelucire types such as, e.g., Gelucire 44/14 etc., Gelucire 50/10, Gelucire 62/05.

A solid solution according to the invention may be prepared according to methods known by a person skilled in the art such as, e.g. by dissolution of the two components (tacrolimus and the water-miscible carrier) in a suitable solvent followed by evaporation of the solvent or it may be prepared by heating one or both of the components to accelerate dissolution of tacrolimus in the carrier or to melt the carrier together with tacrolimus. The above methods are not intended to limit the invention in any way and serve more as illustrative examples. In the following is given a more detailed description

Preparation of a solid solution

Solid solutions (solvent method) can be prepared by dissolving a physical mixture of the active substance (i.e. tacrolimus and/or a derivative thereof) and the carrier in a common organic solvent, followed by evaporation of the solvent. In this case, the carrier is a hydrophilic polymer. Suitable organic solvents include pharmaceutical acceptable solvents in which the active substance is soluble such as methanol, ethanol, methylene chloride, chloroform, ethylacetate, acetone or mixtures thereof.

Suitable water soluble carriers include water-miscible carriers mentioned above.

The solid solution is preferably formed by spray drying techniques, controlled agglomeration, freeze-drying or coating on carrier particles or any other solvent removal process. The dried product contains the active substance present in the form of a solid solution.

As an alternative to the use of organic solvents the drug and polymer may be co-grinded or extruded at elevated temperatures (melt extrusion) or they may be melted together and then (preferably in liquid form) applied to a suitable pharmaceutically acceptable powder.

An especially suitable method is by dissolving tacrolimus in the carrier and then spraying this solution on a powder or powder mixture using a controlled agglomeration method described in WO 03/004001 (by the same Applicant). Stabilizing agents etc. may be added in order to ensure the stability of the solid solution. Details concerning the controlled agglomeration method are given in the above-identified publication, which is hereby incorporated by reference as well as in the Examples herein. In short, the invention provide a process for preparing a particulate pharmaceutical material comprising tacrolimus and/or an analogue thereof which method comprises spraying a first composition in liquid form, said composition preferably being a solid solution of tacrolimus onto a second composition comprising a support, said second composition e.g. being in the fluidised state and having a temperature less than the melting point of the carrier. In principle the active substance may be present in the carrier composition and/or in the second composition. However, in those cases where tacrolimus and/or an analogue thereof should be present in the composition at least partly as a solid dispersion, it is advantageous to incorporate or dissolve tacrolimus and/or an analogue thereof in the carrier composition.

An advantage of using the controlled agglomeration method described in WO 03/004001 is that it is possible to apply a relatively large amount of a melt to a particulate material without having an undesirable growth in particle size. Accordingly, in one embodiment of the invention, the particulate material of a pharmaceutical composition has a geometric weight mean diameter d_{gw} of ≥ 10 μm such as, e.g. ≥ 20 μm, from about 20 to about 2000, from about 30 to about 2000, from about 50 to about 2000, from about 60 to about 2000, from about 75 to about 2000 such as, e.g. from about 100 to about 1500 μm, from about 100 to about 1000 μm or from about 100 to about 700 μm, or at the most about 400 μm or at the most 300 μm such as, e.g., from about 50 to about 400 μm such as, e.g., from about 50 to about 350 μm, from about 50 to about 300 μm, from about 50 to about 250 μm or from about 100 to about 300 μm.

The solid material obtained by the above-mentioned method is in particulate form that has suitable properties with respect to flowability and/or compressibility and is therefore suitable for further processing into pharmaceutical dosage forms.

Pharmaceutical compositions for immediate release

As described above, one of the advantages of a solid solution according to the invention is that it provides a system that can be used in the preparation of several dosage forms and due to the fact that tacrolimus is present in dissolved form and thereby readily releasable it is a suitable system both for immediate release compositions as well as for controlled release compositions. The immediate release compositions may be the solid solution as such or, more preferred, in the form of an oral dosage form wherein the solid solution is present in admixture with pharmaceutically acceptable excipients that do no intend to significally delay the release of tacrolimus from the composition. The topical dosage form would normally be for immediately release. An immediate release composition normally release at least about 50% of tacrolimus contained in the composition within at the most about 2 hours, as determined by a suitable dissolution test such as, e.g., described in Ph. Eur. In a specific aspect, the invention provides a pharmaceutical composition or a solid dosage form that releases tacrolimus and/or an analogue thereof relatively fast so as to enable a relatively fast onset of therapeutic effect. Within the meaning of immediate release is also that at least about 50% w/w of tacrolimus contained in the composition is released within at the most about 1.5 hours such as, e.g., within at the most about 1 hour, within at the most about 0.75 hours or within at the most about 0.5 hours employing a suitable dissolution method. Further examples include that at least about 55% w/w, such as, e.g., at least about 60% w/w, at least about 65% w/w, at least about 70% w/w, at least about 75% w/w, at least about 80% w/w or at least about 85% w/w of tacrolimus is release within at the most about 1.5 hours such as, e.g., within at the most about 1 hour, within at the most about 0.75 hours or within at the most about 0.5 hours employing a suitable dissolution method.

In those cases where the composition is in the form of tablets, an immediate release composition normally has a disintegration time of at the most 60 min such as, e.g., at the most about 45 min, at the most about 30 min, at the most about 15 min or at the most about 10 min when tested according to Ph. Eur.

Release modifying agents

A controlled release composition typically comprises the solid solution in admixture with one or more release modifying agents and, optionally, further one or more pharmaceutically acceptable excipients. Such release modifying agents are typically selected from the group consisting of water-miscible substances including water-miscible polymers, water-insoluble polymers and oils or oily-like materials and, in a specific embodiment the resulting mixture is a solid mixture.

In the present context the terms "controlled release" and "modified release" are intended to be equivalent terms covering any type of release of tacrolimus from a composition of the invention that is appropriate to obtain a specific therapeutic or prophylactic response after administration to a subject. A person skilled in the art knows how controlled release/modified release differs from the release of plain tablets or capsules. The terms "release in a controlled manner" or "release in a modified manner" have the same meaning as stated above.

The terms controlled release/modified release include slow release (that results in a lower C_{max} and later t_{max}, but $t_{½}$ is unchanged), extended release (that results in a lower C_{max}, later t_{max}, but apparent $t_{½}$ is longer); delayed release (that result in an unchanged C_{max}, but lag time and, accordingly, t_{max} is delayed, and $t_{½}$ is unchanged) as well as pulsatile release, burst release, sustained release, prolonged release, chrono-optimized release, fast release (to obtain an enhanced onset of action) etc. Included in the terms is also e.g. utilization of specific conditions within the body e.g. different enzymes or pH changes in order to control the release of the drug substance.

Water-miscible substances

Typically the water-miscible polymer for use as a release modifying agent according to the invention is a cellulose derivative selected from the group consisting of hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), methylcellulose, sodium carboxymethylcellulose, hydroxyethyl cellulose; poloxamers, polyoxyethylene stearates, poly-ϵ-caprolactone, polyvinylpyrrolidone (PVP), polyvinylpyrrolidone-polyvinylacetate copolymer PVP-PVA (Kollidon VA64), poly-methacrylic polymers (Eudragit RS, Eudragit RL, Eudragit NE, Eudragit E), polyvinyl alcohol (PVA), poly(ethylene oxide) (PEO) and the like. In interesting embodiments, the release modifying agent is a cellulose derivative like e.g. hydroxypropyl methylcellulose. Pectinates, alginates galactomannans, xanthan gums

Polar lipids like mono and di glycerides and mixtures thereof and polyglycolised glycerides like Gelucire.

In another aspect of the invention, the water-miscible polymer for use as a release modifying agent is a polymer that has a pH-dependant water-solubility and the polymer is selected from the group consisting of polyacrylamides; phthalate derivatives such as acid phthalates of carbohydrates including amylose acetate phthalate, cellulose acetate phthalate, cellulose acetate terephtahalate, cellulose acetate isophthalate, other cellulose ester phthalates, cellulose ether phthalates, hydroxypropyl cellulose phthalate, hydroxypropylcellulose acetate phthalate, hydroxypropyl ethylcellulose phthalate, hydroxypropyl methylcellulose phthalate (HMPCP), methylcellulose phthalate, methyl cellulose acetate phthalate, polyvinyl acetate phthalate, polyvinyl acetate hydrogen phthalate, sodium cellulose acetate phthalate, starch acid phthalate; phthalates of other compounds including polyvinyl acetate phthalate (PVAP); other cellulose derivatives including hydroxypropyl methylcellulose acetate succinate (HPMCAS), carboxymethylcellulose, cellulose acetate trimellitate; alginates; carbomers; polyacrylic acid derivatives such as acrylic acid and acrylic ester copolymers, polymethacrylic acid and esters thereof, poly acrylic methacrylic acid copolymers, methacrylic acid copolymer (Eudragit L, Eudragit S); styrene-maleic acid dibutyl phthalate copolymer, styrene-maleic acid polyvinylacetate phthalate copolymer, styrene and maleic acid copolymers; shellac, starch glycolate; polacrylin; vinyl acetate and crotonic acid copolymers and the like. Typically these types of polymers delay the release so that no release or only a small amount of tacrolimus is released under conditions corresponding to an acidic pH, i.e. in the stomach; while the release takes place once the composition (or parts thereof) has passed the stomach and entered into the intestines.

Water-insoluble polymers

In a still further embodiment, the release modifying agent is a water-insoluble polymer that is selected from the group consisting of ethyl cellulose, cellulose acetate, cellulose nitrate, and the like.

Oil-like materials

As mentioned above, the release modifying agent may also be an oil or oily-like material such as hydrophilic and hydrophobic oils or oily-like materials. In the present context the term "oils and oily-like materials" is used in a very broad sense including

oils, waxes, semi-solid materials and materials that normally are used as solvents (such as organic solvents) or cosolvents within the pharmaceutical industry. The oils and oily-like materials that can be used as release modifying agents will normally be liquid at ambient or elevated temperature (for practical reasons the max. temperature is about 250 °C). They may be hydrophilic, lipophilic, hydrophobic and/or amphiphilic materials.

The oils and oily-like material that are suitable for use in the present context are substances or materials, which have a melting point of at least about 0 °C and at the most about 250 °C.

In specific embodiments of the invention, the oil or oily-like material has a melting point of about 5 °C or more such as, e.g., about 10 °C or more, about 15 °C or more, about 20 °C or more or about 25 °C or more.

In the present context, the melting point is determined by DSC (Differential Scanning Calorimetry). The melting point is determined as the temperature at which the linear increase of the DSC curve intersects the temperature axis (see Fig. 2 for further details).

Interesting oils or oily-like materials are generally substances, which are used in the manufacture of pharmaceuticals as so-called melt binders or solid solvents (in the form of solid dosage form), or as co-solvents or ingredients in pharmaceuticals for topical use.

It may be hydrophilic, hydrophobic and/or have surface-active properties. In general hydrophilic and/or hydrophobic oils or oily-like materials are suitable for use in the manufacture of a pharmaceutical composition comprising a therapeutically and/or prophylactically active substance that has a relatively low aqueous solubility such as, in the present case, tacrolimus, and/or when the release of the active substance from the pharmaceutical composition is designed to be immediate or non-modified. Hydrophobic oil or oily-like materials, on the other hand, are normally used in the manufacture of a modified release pharmaceutical composition. The above-given considerations are simplified to illustrate general principles, but there are many cases where other combinations of oils or oily-like materials and other purposes are relevant and, therefore, the examples above should not in any way limit the invention.

Typically, a suitable hydrophilic oil or oily-like material is selected from the group consisting of: polyether glycols such as, e.g., polyethylene glycols, polypropylene glycols; polyoxyethylenes; polyoxypropylenes; poloxamers and mixtures thereof, or it may be selected from the group consisting of: naturally occurring polysaccharides, alginate, xanthan gums, pectins, maltose, and mixtures thereof.

A suitable hydrophobic oil or oily-like material may be selected from the group consisting of: straight chain saturated hydrocarbons, sorbitan esters, paraffins; fats and oils such as e.g., cacao butter, beef tallow, lard, vegetable oils, polyether glycol esters; higher fatty acid such as, e.g. stearic acid, myristic acid, palmitic acid, higher alcohols such as, e.g., cetanol, stearyl alcohol, low melting point waxes such as, e.g., glyceryl monostearate, glyceryl monooleate, hydrogenated tallow, myristyl alcohol, stearyl alcohol, substituted and/or unsubstituted monoglycerides, substituted and/or unsubstituted diglycerides, substituted and/or unsubstituted triglycerides, yellow beeswax, white beeswax, carnauba wax, castor wax, japan wax, acetylate monoglycerides; NVP polymers, PVP polymers, acrylic polymers, or a mixture thereof.

The oil or oily-like material may also be a sorbitan ester such as, e.g., sorbitan di-isostearate, sorbitan dioleate, sorbitan monolaurate, sorbitan monoisostearate, sorbitan monooleate, sorbitan monopalmitate, sorbitan monostearate, sorbitan sesqui-isostearate, sorbitan sesquioleate, sorbitan sesquistearate, sorbitan tri-isostearate, sorbitan trioleate, sorbitan tristearate or mixtures thereof.

The oil or oily-like material may of course comprise a mixture of different oils or oily-like materials such as, e.g., a mixture of hydrophilic and/or hydrophobic materials.

Other suitable oils or oily-like materials may be solvents or semi-solid excipients like, e.g. propylene glycol, polyglycolised glycerides including Gelucire 44/14, complex fatty materials of plant origin including theobroma oil, carnauba wax, vegetable oils like e.g. almond oil, coconut oil, corn oil, cottonseed oil, sesame oil, soya oil, olive oil, castor oil, palm kernels oil, peanut oil, rape oil, grape seed oil etc., hydrogenated vegetable oils such as, e.g. hydrogenated peanut oil, hydrogenated palm kernels oil, hydrogenated cottonseed oil, hydrogenated soya oil, hydrogenated castor oil, hydrogenated coconut oil; natural fatty materials of animal origin including beeswax, lanolin, fatty alcohols including cetyl, stearyl, lauric, myristic, palmitic, stearic fatty alcohols; esters including

glycerol stearate, glycol stearate, ethyl oleate, isopropyl myristate; liquid interesterified semi-synthetic glycerides including Miglycol 810/812; amide or fatty acid alcolamides including stearamide ethanol, diethanolamide of fatty coconut acids, acetic acid esters of mono and di-glycerides, citric acid esters of mono and di-glycerides, lactic acid esters of mono and diglycerides, mono and di-glycerides, poly-glycerol esters of fatty acids, poly-glycerol poly-ricinoleate, propylene glycol esters of fatty acids, sorbitan monostearates, sorbitan tristearates, sodium stearoyl lactylates, calcium stearoyl lactylates, diacetyl tartaric acid esters of mono and di-glycerides etc.

Normally, a pharmaceutical composition for controlled release of tacrolimus and/or an analogue thereof has a concentration of the release modifying agent in the composition of about 5% w/w or more such as, e.g., about 10% w/w or more, about 15% w/w or more, about 20% w/w or more, about 25% w/w or more, about 30% w/w or more, about 35% w/w or more, about 40% w/w or more, about 45% w/w or more, about 50 w/w or more, about 55% w/w or more, about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more, about 80% w/w or more, about 85% w/w or more, about 90% w/w or more or about 95% w/w or more.

As mentioned hereinbefore, a specific aspect of the invention relates to the use of a solid solution according to the present invention to provide a controlled release pharmaceutical composition. The choice of the individual components are of importance of the release rate and release pattern obtained, but it is important that the starting point is the solid solution according to the invention in order to obtain a suffiecient bioavailability upon oral administration. In the following are given specific examples of dissolution profiles that may be suitable and that can be provided by a suitable combination of the specific types of pharmaceutically acceptable ingredients as well as the amounts thereof. The compositions described herein may of course be provided with an appropriate coating, i.e. a film coating in order to improve patient acceptability or in order to control the release rate e.g. by use of a water-insoluble but water-permeable coating or e.g. by enteric coatings. A person skilled in the art knows how to obtain coated compositions and how to choose suitable coating materials.

Controlled release pharmaceutical compositions

There is a need for developing pharmaceutical tacrolimus-containing compositions notably for oral use that lead to an improved treatment of conditions with tacrolimus. An improved release profile, which can ensure significant lower C_{max}, but still good

bioavailability, as well as an extended release of drug staying within the therapeutic plasma levels for up to 24 hours after administration. A further therapeutic improvement of the invention is the reduction in food effect, which together with the improved absorption should give more reproducible plasma levels. The therapeutic improvements of the invention will clearly improve the ratio between side effects and efficacy.

Moreover, the inventors have found that the efficacy of oral tacrolimus treatment can be greatly improved through design of the tacrolimus release profile. On the one hand relatively high doses of tacrolimus are required to avoid transplant rejection and on the other hand side effects often get too pronounced even at therapeutically relevant levels. Thus, the side effects acute nausea, vomiting, nephrotoxicity and neurotoxicity are directly linked to high peak plasma concentrations. This link has been demonstrated in dogs. In those cases where a lower dose has been used in order to avoid a high peak level, the dose-dependent side effects almost cease to occur at a certain threshold level and, if they occurred, they were much less pronounced. However, due to the decrease in dose (without increasing the bioavailability) the therapeutically effective level is only maintained for a short duration of time. The present invention addresses this problem by providing a pharmaceutical composition containing tacrolimus, wherein the release of tacrolimus is designed to avoid high peak concentrations and at the same time, the composition is designed so that the overall bioavailability is maintained or increased (compared to commercially available tacrolimus-containing tablets). Moreover, by delaying the release of tacrolimus and at the same time provide a composition wherein tacrolimus is at least partly on dissolved form, it is possible to obtain a significant absorption in the distal part of the gastrointestinal tract.

Use of a solid solution according to the present invention serves as a suitable basic material to provide pharmaceutical compositions and solid dosage forms for improved treatment of conditions that respond to tacrolimus treatment, especially to controlled release compositions.

In one aspect, the present invention relates to a pharmaceutical composition comprising the solid solution of tacrolimus and/or an analogue thereof and the water-miscible carrier admixed with one or more pharmaceutically acceptable excipient, wherein the composition upon oral administration to a mammal in need thereof exhibits

an AUC/$AUC_{Prograf®}$ value of at least about 1.3, the AUC values being determined under similar conditions.

As it appears from the Examples herein the bioavailability obtained after administration of a composition according to the invention is markedly improved. Thus, in specific embodiments, the AUC/$AUC_{Prograf®}$ value is at least about 1.5 such as about 1.75 or more, about 1.8 or more, about 1.9 or more, about 2.0 or more, about 2.5 or more, about 2.75 or more, about 3.0 or more, about 3.25 or more, about 3.5 or more, about 3.75 or more, about 4.0 or more, about 4.25 or more, about 4.5 or more, about 4.75 or more or about 5.0 or more, the AUC values being determined under similar conditions.

After oral administration of a pharmaceutical composition according to the present invention it is contemplated that the plasma concentration versus time profile show an extended period of time in which the plasma concentration is maintained within the therapeutic window (i.e. the plasma concentration leads to a therapeutic effect) without leading to serious unwanted side effects. Thus, a reduction in peak concentration is also observed. Accordingly, the invention relates to a pharmaceutical composition in particulate form comprising tacrolimus together with one or more pharmaceutically acceptable excipient, wherein the composition upon oral administration to a mammal in need thereof releases tacrolimus in a controlled manner and exhibits a C_{max} that is at the most about 80% of that of C_{max} for Prograf® tablets such as, e.g., at the most about 75%, at the most about 70%, at the most about 65%, at the most about 60%, at the most about 55%, at the most about 50%, at the most about 45% or at the most about 40%.

In the present context the terms controlled release and modified release are intended to be equivalent terms covering any type of release of tacrolimus from a composition of the invention that is appropriate to obtain a specific therapeutic or prophylactic response after administration to a subject. A person skilled in the art knows how controlled release/modified release differs from the release of plain tablets or capsules. The terms "release in a controlled manner" or "release in a modified manner" have the same meaning as stated above.

The terms controlled release/modified release include slow release (that results in a lower C_{max} and later t_{max}, but $t_{½}$ is unchanged), extended release (that results in a lower C_{max}, later t_{max}, but apparent $t_{½}$ is longer); delayed release (that result in an unchanged

C_{max}, but lag time and, accordingly, t_{max} is delayed, and $t_{½}$ is unchanged) as well as pulsatile release, burst release, sustained release, prolonged release, chrono-optimized release, fast release (to obtain an enhanced onset of action) etc. Included in the terms is also e.g. utilization of specific conditions within the body e.g. different enzymes or pH changes in order to control the release of the drug substance.

To be more specific, after oral administration to a mammal, including a human, of a pharmaceutical composition according to the present invention containing a dose of 5 mg tacrolimus, tacrolimus is released in a controlled manner and will exhibit a C_{max} that is at the most about 30 ng/ml such as, e.g. at the most about 25 ng/ml or at the most about 20 ng/ml.

However, a reduction in peak concentration may not lead to a decrease in therapeutic effect as long as the plasma concentration of tacrolimus is maintained within the therapeutic window. Accordingly, the present invention also relates to a pharmaceutical composition, wherein W_{50} is at least about 2 hours, such as, e.g., at least about 3 hours, at least about 4 hours, at least about 5 hours, at least about 6 hours, at least about 7 hours, at least about 8 hours, at least about 9 hours, about 10 hours or more, about 11 hours or more, about 12 hours or more, about 13 hours or about 14 hours or more.

Furthermore or moreover, a composition according to the invention has a $C_{diff} = [C_{max} - C_t (t=12 \text{ hours})]$ that is less than that of Prograf® tablets under the same conditions. If C_{diff} for Prograf® tablets is set to 100 then C_{diff} of a composition according to the invention is normally 90 or less such as, e.g., about 85 or less, about 80 or less, about 75 or less, about 70 or less, about 65 or less, about 60 or less, about 55 or less, about 50 or less, about 45 or less or about 40 or less.

More specifically, after oral administration to a mammal, including a human, of a pharmaceutical composition of the invention containing 5 mg of tacrolimus, tacrolimus is released in a controlled manner and exhibits a C_{diff} of about 20 ng/ml or less such as, e.g., about 15 ng/ml or less, about 13 ng/ml or less or about 10 ng/ml or less.

A pharmaceutical composition according to the invention releases tacrolimus in a controlled manner in order to extend the therapeutic action of tacrolimus. In one aspect the release may be pH dependant, i.e. the release predominantly takes place after

passage of the stomach. Such a pH dependent release is mainly provided by means of enteric coating material as described herein (polymers that have a pH-dependant solubility). The release may also be pH independent, e.g. by providing the composition with a controlled release coating such as, e.g. a cellulose based coating like e.g. ethylcellulose or by providing the composition in the form of a matrix composition such as, e.g., a hydrophilic cellulose polymer matrix type e.g. based on HPMC. A combination may of course also be employed.

In general, the change in bioavailability and/or the changes in other bioavailability related parameters are normally determined by *in vivo* studies in a suitable animal model testing the compositions in question together with e.g. Prograf® or a similar commercially available tacrolimus-containing product. The use of a dog model for establishing evidence of the bioavailability of certain formulations is general practice in the pharmaceutical industry.

The studies relevant for tacrolimus are non-radomized, cross-over studies, where each dog is it's own control. Four dogs, and four treatments are normally applied. As no iv injections are given, the bioavailabilities obtained are relative.

Further it has surprisingly been found that the need for simultaneous food intake in order to secure a sufficient uptake of tacrolimus is significantly reduced or even completely abolished.

Thus, the pharmaceutical compositions according to the invention provide significant higher bioavailability of tacrolimus, which may reduce the number of daily administered dosage units, and reduce or abolish the need for administration in connection with food intake, which provide for a higher degree of freedom for the recipient of the pharmaceutical compositions, and consequently the patients acceptance and/or compliance may be significantly improved. Furthermore, the compositions provide a significant reduction in side effects, especially side effect related to a high peak concentration (such as, e.g., nephro- and neuro-toxicity, diarrhea, constipation, abdominal pain, nausea etc) and provide for an extended release of tacrolimus leading to a better therapy.

As mentioned above, one of the major challenges with respect to formulation of tacrolimus compositions is to avoid an adverse food effect. In general, tacrolimus is

much better absorbed when it is administered orally without food. A great variation in bioavailability is therefore seen following administration with or without food. This dependency makes it difficult to give precise guidelines as to how large a dose that should be administered and, furthermore, it requires information to the patient about the dosing regime. The present invention aims at providing compositions wherein the adverse food effect is reduced. Thus, the present invention provides a composition, which does not exhibit a significant adverse food effect after administration of the composition to a mammal in need of such a treatment as evidenced by a value of (AUC_{fed}/AUC_{fasted}) of at least about 0.85 with a lower 90% confidence limit of at least 0.75.

More specifically, a pharmaceutical composition according to the invention has a value of (AUC_{fed}/AUC_{fasted}) of about 0.9 or more such as, e.g., about 0.95 or more, about 0.97 or more or about 1 or more such as, e.g., up to about 1.1 or up to about 1.2.

A further advantage of a composition of the present invention is the possibility of obtaining an effective therapeutic response with a decreased dosage compared to traditional oral treatment. Accordingly, upon oral administration to a mammal in need thereof a pharmaceutical composition according to the invention releases tacrolimus or an analogue thereof in a controlled manner and the composition is essentially bioequivalent with Prograf® or a similar commercially available tacrolimus-containing product when administered in a dose that is at the about most about 85% w/w such as, e.g., at the most about 80% w/w, at the most about 75%, at the most about 70% w/w, at the most about 65% w/w, at the most about 60% w/w, at the most about 55% w/w or at the most about 50% w/w of the dose of tacrolimus administered in the form of Prograf® or a similar commercially available tacrolimus-containing product.

Parameters often used in bioequivalence studies are t_{max}, c_{max}, $AUC_{0\text{-}Infinity}$, $AUC_{0\text{-}t}$. Other relevant parameters may be W_{50}, W_{75} and/or MRT. Accordingly, at least one of these parameters may be applied when determining whether bioequivalence is present. Furthermore, in the present context, two compositions are regarded as bioequivalent if value of the parameter used is within 80-125% of that of Prograf® or a similar commercially available tacrolimus-containing product used in the test.

In the present context "t_{max}" denotes the time to reach the maximal plasma concentration (c_{max}) after administration; $AUC_{0\text{-}Infinity}$ denotes the area under the plasma

concentration versus time curve from time 0 to infinity; AUC_{0-t} denotes the area under the plasma concentration versus time curve from time 0 to time t; W_{50} denotes the time where the plasma concentration is 50% or more of C_{max}; W_{75} denotes the time where the plasma concentration is 75% or more of C_{max}; and MRT denotes mean residence time for tacrolimus (and/or an analogue thereof).

Two other main disadvantages associated with treatment or prophylaxis with tacrolimus is the relative high incidence of side effects and a relatively high inter-individual variation. It is envisaged that a composition according to the invention will lead to a reduction in side effects. The reduction may be in terms of reduced frequency or in terms of severity. The side effects in question include e.g. nephro- and neuro-toxicity, diarrhe, constipation, abdominal pain, nausea etc. In one aspect the invention concerns a pharmaceutical composition in particulate form comprising tacrolimus or an analogue thereof together with one or more pharmaceutically acceptable excipient, wherein the composition upon oral administration to a mammal in need thereof releases tacrolimus or an analogue thereof in a controlled manner and reduces side effects compared to those of Prograf® administered under the same conditions and in a dose that provides an equivalent therapeutic effect.

Increasing the bioavailability, the Area Under the Curve, will normally reduce the intra- and inter- variability related to absorption of a drug substance. This is particularly true; whenever the low and impaired bioavailability is a consequence of poor water solubility. It is contemplated that compositions according to the invention will provide CV's (CV = coefficient of variation) on Area under Curve data that are significantly smaller than with Prograf® and like products.

As mentioned hereinbefore, one of the basic features of the present invention is that it is possible to obtain an improvement in the bioavailability by oral administration of a composition of the present invention. Normally, a low bioavailability of a drug substance after oral administration is a barrier for design of a controlled or modified release composition of the drug substance due to the fact that it is almost impossible to obtain effective drug levels over a prolonged period of time. However, with the present technology it is possible to obtain a significantly improved bioavailability and thereby possible to design controlled, modified or delayed release compositions.

Tacrolimus is extensively metabolized by the CYP3A4 isoenzyme in the gut wall and liver. Accordingly, a suitable controlled release composition may be a composition that is designed to release tacrolimus in a delayed manner so as to avoid or reduce the CYP3A4 metabolism in the gastrointestinal tract.

Delayed release is mainly brought about by some kind of enteric coating. Whereas semipermeable coating will show some kind of delayed release, it does not preciously enough "delay" release. Additionally it requires a certain amount of time to release the content. The coating sought for this invention, is a pH dependant coating. This type of coating is very resistant to release of drug until a certain pH is reached. Within very few 1/10'th of pH, the film alters properties and becomes permeable. Examples of pH-sensitive polymers are mentioned hereinbefore. However, pH-sensitive polymers of specific interest include shellac; phthalate derivatives, particularly cellulose acetate phthalate, polyvinylacetate phthalate, and hydroxypropylmethylcellulose phthalate; polyacrylic acid derivatives, particularly polymethyl methacrylate blended with acrylic acid and acrylic ester copolymers; and vinyl acetate and crotonic acid copolymers.

The release of the active substance from a composition having a delayed release coating could also be an enzymatic reaction, if for example Zein or mono/di-glyceride mixtures are employed as coating material.

Upon oral administration to a mammal, including a human, in need thereof, a controlled release pharmaceutical composition according to the present invention releases tacrolimus in such a manner that a plasma concentration of at least about 5 ng/ml such as, e.g., at least about 7.5 ng/ml or at least about 10 ng/ml for a time period of at least about 24 hours is obtained. In a specific aspect of the invention the difference between the peak plasma concentration and plasma concentration measured 24 hours after administration is at the most about 20 ng/ml such as, e.g., at the most about 10 ng/ml, at the most about 7.5 ng/ml or at the most about 5 ng/ml.

In the following is given examples of compositions having suitable release profiles.

In one aspect, the invention relates to a pharmaceutical composition comprising tacrolimus and/or an analogue thereof together with one or more pharmaceutically acceptable excipient, wherein the composition upon oral administration to a mammal in need thereof in a controlled manner releases at least about 80% w/w within 0.75 hours or more, such as, e.g., at least about 50% w/w of the total amount of tacrolimus or an

analogue thereof within about 24 hours, such as, e.g., within about 22 hours, within about 20 hours, within about 18 hours, within about 15 hours or within about 12 hours.

In a further embodiment at the most about 60% w/w such as, e.g., at the most 62% w/w, at the most about 65% w/w or at the most about 70% w/w tacrolimus is released 15 hours after oral administration to a mammal of a composition according to the invention or, alternatively, when tested in a suitable in vitro dissolution test, 15 hours after start of such a test.

More specifically, upon oral administration to a mammal in need thereof a composition according to the invention releases at least about 50% w/w of the total amount of tacrolimus and/or an analogue thereof within about 10 hours such as, e.g., within about 8 hours, within about 6 hours, within about 4 hours or within about 3 hours.

In another embodiment, upon oral administration to a mammal in need thereof, a pharmaceutical composition according to the invention releases at least 80% w/w tacrolimus after about 0.5 hours or more such as, e.g., after about 0.75 hours or more, about 1 hour or more, about 2 hours or more, about 3 hours or more, about 4 hours or more or about 5 hours or more; or alternatively, when tested in a suitable in vitro dissolution test releases at least 80% w/w after about 0.5 hours or more such as, e.g., after about 0.75 hours or more, about 1 hour or more, about 2 hours or more, about 3 hours or more, about 4 hours or more or about 5 hours or more after start of the test.

In a further embodiment, upon oral administration to a mammal in need thereof a pharmaceutical composition according to the invention releases at least about 55% w/w such as, e.g., about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more or about 80% w/w or more of the total amount of tacrolimus and/or an analogue thereof within about 24 hours, such as, e.g., within about 22 hours, within about 20 hours, within about 18 hours, about 15 hours, within about 12 hours, within about 10 hours, within 8 hours or within about 6 hours.

Furthermore or alternatively, at least about 50% w/w of the total amount of tacrolimus and/or an analogue thereof is released about 24 hours, within about 22 hours, within about 20 hours, within about 18 hours, within 15 hours, within about 12 hours, when tested in an in vitro dissolution test and employing a dissolution medium comprising a buffer having pH 7.5. Guidance for a suitable dissolution test is described in the

Examples herein, but variations with respect to the specific method employed and the ingredients contained in the dissolution medium etc. are within the scope of the present invention. A person skilled in the art will know how to carry out a suitable dissolution test e.g. with guidance from USP, Ph.Eur. and the like. Suitable conditions for the *in vitro* dissolution test are employing USP dissolution test (paddle method) and a buffer pH 7.5 containing 2.5% SDS and 1g/mL of pancreatin as dissolution medium.

In other embodiments, the following conditions are fulfilled with respect to *in vitro* dissolution test:

i) at least about 50% w/w of the total amount of tacrolimus or an analogue thereof is released within about 10 hours such as, e.g., within about 8 hours, within about 6 hours, within about 4 hours, within about 3 hours, within about 2 hours, within about 1 hour, within about 45 min, within about 30 min or within about 15 min, when tested in an in vitro dissolution test and employing a dissolution medium comprising a buffer having pH 7.5

ii) at least about 50% w/w of the total amount of tacrolimus or an analogue thereof is released within about 1.5 hours such as, e.g., within about 1 hour, within about 0.75 hours, within about 0.5 hours or within about 20 minutes, when tested in an in vitro dissolution test and employing a dissolution medium comprising a buffer having pH 7.5.

iii) at least about 55% w/w such as, e.g., about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more or about 80% w/w or more of the total amount of tacrolimus or an analogue thereof is released within about 15 hours such as, e.g., within about 12 hours, within about 10 hours, within 8 hours or within about 6 hours, when tested in an in vitro dissolution test and employing a dissolution medium comprising a buffer having pH 7.5

iv) at least about 55% w/w such as, e.g., about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more or about 80% w/w or more of the total amount of tacrolimus or an analogue thereof is released within about 5 hours such as, e.g., within about 4 hours, within about 3 hours, within about 2 hours, within about 1 hours or within about 30 minutes, when tested in an in vitro dissolution test and employing a dissolution medium comprising a buffer having pH 7.5, and/or

v) at least about 20% w/w such as, e.g., at least about 25% w/w, at least about 30% w/w, at least about 35% w/w or at least about 40% w/w of the total amount of tacrolimus or an analogue thereof is released within the first 3 hours such as, e.g., within the first 2 hours or within the first hour when tested in an in vitro dissolution test and employing a dissolution medium comprising a buffer having pH 7.5.

In an interesting embodiment, the composition is designed to have a delayed release of tacrolimus and/or an analogue thereof. Therefore, the invention also includes a pharmaceutical composition in particulate form comprising tacrolimus and/or an analogue thereof together with one or more pharmaceutically acceptable excipient, wherein the composition upon oral administration to a mammal in need thereof has a delayed release of tacrolimus and/or an analogue thereof so that at the most 10% w/w such as, e.g., at the most about 7.5% w/w or at the most about 5% w/w of the total amount of tacrolimus or an analogue thereof is released within the first two hours such as, e.g., within the first hour after administration.

In other embodiments, the following conditions are fulfilled with respect to *in vitro* dissolution test performed under acidic conditions:

i) at the most about 30% w/w such as, e.g., at the most about 25% w/w, at the most about 20% w/w, at the most about 15% w/w or at the most about 10% w/w of tacrolimus or an analogue thereof is released within 2 hours in an in vitro dissolution test employing a dissolution medium having a pH of at the most about 5 such as, e.g. at the most about 4.5, at the most about 4, at the most about 3.5, at the most about 3, at the most about 2 or at the most about 1.5,

ii) at the most about 10% w/w such as, e.g., at the most about 7.5% w/w, at the most about 5% w/w or at the most about 2.5% w/w of tacrolimus or an analogue thereof is released within 2 hours in an in vitro dissolution test employing a dissolution medium having a pH of at the most about 5 such as, e.g. at the most about 4.5, at the most about 4, at the most about 3.5, at the most about 3, at the most about 2 or at the most about 1.5

iii) at the most about 60% w/w such as, e.g., at the most about 50% w/w, at the most about 40% w/w or at the most about 30% w/w of tacrolimus or an analogue thereof is released within 15 hours such as, e.g., within about 12 hours, when tested in an in vitro

dissolution test employing a dissolution medium having a pH of at the most about 4.5 such as, e.g. at the most about 4.0, at the most about 3.5, at the most about 3, at the most about 2 or at the most about 1.5

iv) at the most about 40% w/w such as, e.g., at the most about 30% w/w, at the most about 25% w/w or at the most about 20% w/w of tacrolimus or an analogue thereof is released within 6 hours when tested in an in vitro dissolution test employing a dissolution medium having a pH of at the most about 4.5 such as, e.g. at the most about 4.0, at the most about 3.5, at the most about 3, at the most about 2 or at the most about 1.5,

v) at the most about 30% w/w such as, e.g., at the most about 25% w/w, at the most about 20% w/w or at the most about 15% w/w of tacrolimus or an analogue thereof is released within 4 hours when tested in an in vitro dissolution test employing a dissolution medium having a pH of at the most about 4.5 such as, e.g. at the most about 4.0, at the most about 3.5, at the most about 3, at the most about 2 or at the most about 1.5, and/or

vi) less than 63.2% w/w of tacrolimus or an analogue thereof is released after 15 hours when tested in an in vitro dissolution test employing a dissolution medium having a pH of at the most about 4.5 such as, e.g. at the most about 4.0, at the most about 3.5, at the most about 3, at the most about 2 or at the most about 1.5.

Apart from tacrolimus, a composition of the invention may also comprise a further therapeutically, prophylactically and/or diagnostically active substance. Notably combinations of tacrolimus with at least one of the following active substances are of interest: Substances that are indicated for use in connection with organ transplantation such as, e.g., steroids, calcineurin inhibitors and/or anti-proliferative agents. Specific examples include prednisone, prednisolone, methylprednisone, cyclosporin, mycophenolate, azathioprine, everolimus, mycophenolate sodium, FTY720 from Novartis and sirolimus.

Pharmaceutically acceptable excipients

As mentioned before, a solid solution according to the invention is especially suitable for processing into oral dosage from, e.g. involving a step of spraying the solid solution onto one or more suitable pharmaceutically acceptable excipients (optionally in

admixture with other substances like e.g. other therapeutically active substances etc). In the present context the terms "pharmaceutically acceptable excipient" are intended to denote any material, which is inert in the sense that it substantially does not have any therapeutic and/or prophylactic effect *per se*. Such an excipient may be added with the purpose of making it possible to obtain a pharmaceutical, cosmetic and/or foodstuff composition, which have acceptable technical properties.

Especially dosage forms for oral administration are of interest e.g. tablets, sachets, capsules etc. A person skilled in the art know how to produce suitable dosage form e.g. with reference to Remington's Pharmaceutical Science.

Examples on suitable excipients for use in a composition or solid dosage form according to the invention include fillers, diluents, disintegrants, binders, lubricants etc. or mixture thereof. As the composition or solid dosage form according to the invention may be used for different purposes, the choice of excipients is normally made taken such different uses into considerations. Other pharmaceutically acceptable excipients for suitable use are e.g. acidifying agents, alkalizing agents, preservatives, antioxidants, buffering agents, chelating agents, coloring agents, complexing agents, emulsifying and/or solubilizing agents, flavors and perfumes, humectants, sweetening agents, wetting agents etc.

Examples on suitable fillers, diluents and/or binders include lactose (e.g. spray-dried lactose, α-lactose, β-lactose, Tabletose®, various grades of Pharmatose®, Microtose® or Fast-Floc®), microcrystalline cellulose (various grades of Avicel®, Elcema®, Vivacel®, Ming Tai® or Solka-Floc®), hydroxypropylcellulose, L-hydroxypropylcellulose (low substituted), hydroxypropyl methylcellulose (HPMC) (e.g. Methocel E, F and K, Metolose SH of Shin-Etsu, Ltd, such as, e.g. the 4,000 cps grades of Methocel E and Metolose 60 SH, the 4,000 cps grades of Methocel F and Metolose 65 SH, the 4,000, 15,000 and 100,000 cps grades of Methocel K; and the 4,000, 15,000, 39,000 and 100,000 grades of Metolose 90 SH), methylcellulose polymers (such as, e.g., Methocel A, Methocel A4C, Methocel A15C, Methocel A4M), hydroxyethylcellulose, sodium carboxymethylcellulose, carboxymethylene, carboxymethylhydroxyethylcellulose and other cellulose derivatives, sucrose, agarose, sorbitol, mannitol, dextrins, maltodextrins, starches or modified starches (including potato starch, maize starch and rice starch), calcium phosphate (e.g. basic calcium phosphate, calcium hydrogen

phosphate, dicalcium phosphate hydrate), calcium sulfate, calcium carbonate, sodium alginate, collagen etc.

Specific examples of diluents are e.g. calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, microcrystalline cellulose, powdered cellulose, dextrans, dextrin, dextrose, fructose, kaolin, lactose, mannitol, sorbitol, starch, pregelatinized starch, sucrose, sugar etc.

Specific examples of disintegrants are e.g. alginic acid or alginates, microcrystalline cellulose, hydroxypropyl cellulose and other cellulose derivatives, croscarmellose sodium, crospovidone, polacrillin potassium, sodium starch glycolate, starch, pregelatinized starch, carboxymethyl starch (e.g. Primogel® and Explotab®) etc.

Specific examples of binders are e.g. acacia, alginic acid, agar, calcium carrageenan, sodium carboxymethylcellulose, microcrystalline cellulose, dextrin, ethylcellulose, gelatin, liquid glucose, guar gum, hydroxypropyl methylcellulose, methylcellulose, pectin, PEG, povidone, pregelatinized starch etc.

Glidants and lubricants may also be included in the composition. Examples include stearic acid, magnesium stearate, calcium stearate or other metallic stearate, talc, waxes and glycerides, light mineral oil, PEG, glyceryl behenate, colloidal silica, hydrogenated vegetable oils, corn starch, sodium stearyl fumarate, polyethylene glycols, alkyl sulfates, sodium benzoate, sodium acetate etc.

Other excipients which may be included in a composition or solid dosage form of the invention are e.g. flavoring agents, coloring agents, taste-masking agents, pH-adjusting agents, buffering agents, preservatives, stabilizing agents, anti-oxidants, wetting agents, humidity-adjusting agents, surface-active agents, suspending agents, absorption enhancing agents, agents for modified release etc.

Other additives in a composition or a solid dosage form according to the invention may be antioxidants like e.g. ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorous acid, monothioglycerol, potassium metabisulfite, propyl gallate, sodium formaldehylde sulfoxylate, sodium metabisulfite, sodium thiosulfate, sulfur dioxide, tocopherol, tocopherol acetate, tocopherol hemisuccinate, TPGS or other tocopherol derivatives, etc. The carrier composition may

also contain e.g. stabilising agents. The concentration of an antioxidant and/or a stabilizing agent in the carrier composition is normally from about 0.1 % w/w to about 5% w/w.

A composition or solid dosage form according to the invention may also include one or more surfactants or substances having surface-active properties. It is contemplated that such substances are involved in the wetting of the slightly soluble active substance and thus, contributes to improved solubility characteristics of the active substance.

Examples on surfactants are given in the following.

Suitable excipients for use in a composition or a solid dosage form according to the invention are surfactants such as, e.g., amphiphillic surfactants as those disclosed in WO 00/50007 in the name of Lipocine, Inc. Examples on suitable surfactants are

i) polyethoxylated fatty acids such as, e.g. fatty acid mono- or diesters of polyethylene glycol or mixtures thereof such as, e.g. mono – or diesters of polyethylene glycol with lauric acid, oleic acid, stearic acid, myristic acid, ricinoleic acid, and the polyethylene glycol may be selected from PEG 4, PEG 5, PEG 6, PEG 7, PEG 8, PEG 9, PEG 10, PEG 12, PEG 15, PEG 20, PEG 25, PEG 30, PEG 32, PEG 40, PEG 45, PEG 50, PEG 55, PEG 100, PEG 200, PEG 400, PEG 600, PEG 800, PEG 1000, PEG 2000, PEG 3000, PEG 4000, PEG 5000, PEG 6000, PEG 7000, PEG 8000, PEG 9000, PEG 1000, PEG 10,000, PEG 15,000, PEG 20,000, PEG 35,000,

ii) polyethylene glycol glycerol fatty acid esters, i.e. esters like the above-mentioned but in the form of glyceryl esters of the individual fatty acids;

iii) glycerol, propylene glycol, ethylene glycol, PEG or sorbitol esters with e.g. vegetable oils like e.g. hydrogenated castor oil, almond oil, palm kernel oil, castor oil, apricot kernel oil, olive oil, peanut oil, hydrogenated palm kernel oil and the like,

iv) polyglycerized fatty acids like e.g. polyglycerol stearate, polyglycerol oleate, polyglycerol ricinoleate, polyglycerol linoleate,

v) propylene glycol fatty acid esters such as, e.g. propylene glycol monolaurate, propylene glycol ricinoleate and the like,

vi) mono- and diglycerides like e.g. glyceryl monooleate, glyceryl dioleae, glyceryl mono- and/or dioleate, glyceryl caprylate, glyceryl caprate etc.;

vii) sterol and sterol derivatives;

viii) polyethylene glycol sorbitan fatty acid esters (PEG-sorbitan fatty acid esters) such as esters of PEG with the various molecular weights indicated above, and the various Tween ® series;

ix) polyethylene glycol alkyl ethers such as, e.g. PEG oleyl ether and PEG lauryl ether;

x) sugar esters like e.g. sucrose monopalmitate and sucrose monolaurate;

xi) polyethylene glycol alkyl phenols like e.g. the Triton® X or N series;

xii) polyoxyethylene-polyoxypropylene block copolymers such as, e.g., the Pluronic® series, the Synperonic® series, Emkalyx®, Lutrol®, Supronic® etc. The generic term for these polymers is "poloxamers" and relevant examples in the present context are Poloxamer 105, 108, 122, 123, 124, 181, 182, 183, 184, 185, 188, 212, 215, 217, 231, 234, 235, 237, 238, 282, 284, 288, 331, 333, 334, 335, 338, 401, 402, 403 and 407;

xiii) sorbitan fatty acid esters like the Span® series or Ariacel® series such as, e.g. sorbinan monolaurate, sorbitan monopalmitate, sorbitan monooleate, sorbitan monostearate etc.;

xiv) lower alcohol fatty acid esters like e.g. oleate, Isopropyl myristate, isopropyl palmitate etc.;

xv) ionic surfactants including cationic, anionic and zwitterionic surfactants such as, e.g. fatty acid salts, bile salts, phospholipids, phosphoric acid esters, carboxylates, sulfates and sulfonates etc.

When a surfactant or a mixture of surfactants is present in a composition or a solid dosage form of the invention, the concentration of the surfactant(s) is normally in a range of from about 0,1 – 80% w/w such as, e.g., from about 0.1 to about 20% w/w, from about 0.1 to about 15% w/w, from about 0.5 to about 10% w/w, or alternatively, from about 0.10 to about 80% w/w such as, e.g. from about 10 to about 70% w/w, from about 20 to about 60% w/w or from about 30 to about 50% w/w.

In a specific aspect of the invention, the at least one of the one or more pharmaceutically acceptable excipient is selected from the group consisting of silica acid or a derivative or salt thereof including silicates, silicon dioxide and polymers thereof; magnesium aluminosilicate and/or magnesium aluminometasilicate, bentonite, kaolin, magnesium trisilicate, montmorillonite and/or saponite.

Such materials are is especially useful as a sorption material for oils or oily-like materials in pharmaceuticals, cosmetics and/or foodstuff. In a specific embodiment, the material is used as a sorption material for oils or oily-like materials in pharmaceuticals. The material that has the ability to function as a sorption material for oils or oily-like materials is also denoted "oil sorption material". Furthermore, in the present context the term "sorption" is used to denote "absorption" as well as "adsorption". It should be understood that whenever one of the terms is used it is intended to cover the phenomenon absorption as well as adsorption.

Notably, the pharmaceutically acceptable excipient may comprise a silica acid or a derivative or salt thereof such as, e.g., silicon dioxide or a polymer thereof as a pharmaceutically acceptable excipient. Dependent on the quality employed a silicon dioxide may be a lubricant or it may be an oil sorption material. Qualities fulfilling the latter function seem to be most important.

In a specific embodiment, a composition or solid dosage form according to invention comprises a pharmaceutically acceptable excipient that is a silicon dioxide product that has properties corresponding to Aeroperl® 300, (available from Degussa, Frankfurt, Germany).

As it appears from the examples herein, a very suitable material is Aeroperl® 300 (including materials with properties like or corresponding to those of Aeroperl® 300).

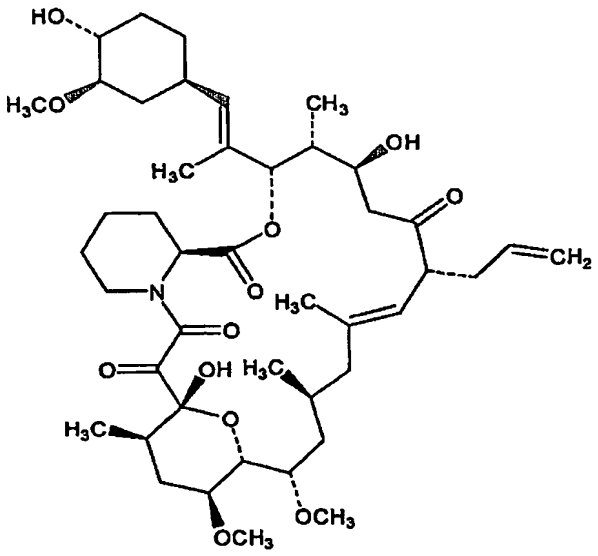
Use of an oil sorption material in compositions or dosage forms according to the invention is very advantageous for the preparation of pharmaceutical, cosmetic, nutritional and/or food compositions, wherein the composition comprises oil or an oily-like material e.g. functioning as a release modifying agent. One of the advantages is that is it possible to incorporate a relatively large amount of oil and oily-like material and still have a material that is solid. Thus, it is possible to prepare solid compositions with a relatively high load of oil or oily-like materials by use of an oil sorption material according to the invention. Within the pharmaceutical field it is an advantage to be able to incorporate a relatively large amount of an oil or an oily-like material in a solid composition especially in those situation where the active substance does not have suitable properties with respect to water solubility (e.g. poor water solubility), stability in aqueous medium (i.e. degradation occurs in aqueous medium), oral bioavailability (e.g. low bioavailability) etc., or in those situations where it is desired to modify the release of an active substance from a composition in order to obtain a controlled, delayed,

sustained and/or pulsed delivery of the active substance. Thus, in a specific embodiment it is used in the preparation of pharmaceutical compositions.

The oil sorption material for use in the processing into solid compositions normally absorbs about 5% w/w or more, such as, e.g., about 10% w/w or more, about 15% w/w or more, about 20% w/w or more, about 25% w/w or more, about 30% w/w or more, about 35% w/w or more, about 40% w/w or more, about 45% w/w or more, about 50 w/w or more, about 55% w/w or more, about 60% w/w or more, about 65% w/w or more, about 70% w/w or more, about 75% w/w or more, about 80% w/w or more, about 85% w/w or more, about 90% w/w or more or about 95% w/w or more of an oil or an oily material and is still a solid material.

Clinical indications and use of compositions according to the invention

Tacrolimus or FK-506 or FR-900506 has the tricyclic structure shown below.



$C_{44}H_{69}NO_{12}$

Tacrolimus appears in the form of white crystals or crystalline powder. It is practically insoluble in water, freely soluble in ethanol and very soluble in methanol and chloroform.

The preparation of tacrolimus is described in EP-A-0 184 162 and analogues of tacrolimus are disclosed e.g. in EP-A-0 444 659 and US 6,387,918, which is hereby incorporated by reference.

Tacrolimus is a macrolide compound with useful immunosuppressive activity, antimicrobial activity and other pharmacological activities and is of value for the treatment or prevention of rejection reactions by transplantation of organs or tissues, graft versus host diseases, autoimmune diseases and infectious diseases. Tacrolimus prolongs the survival of the host and transplanted graft in animal transplant models of liver, kidney, heart, bone marrow and small bowel and pancreas, lung and trachea, skin, cornea and limb.

In animals, tacrolimus has been demonstrated to suppress some humoral immunity and, to a greater extent, cell-mediated reactions such as allograft rejection, delayed type hypersensitivity, collagen-induced arthritis, experimental allergic encephalomyelitis and graft-versus-host disease.

Tacrolimus inhibits T-lymphocyte activation, although the exact mechanism of action is not known. Experimental evidence suggest that tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin inhibited. This effect may prevent the dephosphorylation and translocation of nuclear factor of activated T-cells, a nuclear component thought to initiate gene transcription for the formation of lymphokines. The net result is the inhibition of T-lymphocyte activation, i.e. immunosupression.

A commercially available tacrolimus-containing product is Prograf®. Prograf® is indicated for the prophylaxis of organ rejection in patients receiving allogeneic liver or kidney transplants.

Usually tacrolimus is administered orally and is therefore absorbed from the gastrointestinal tract. It has been observed that the absorption is negatively influenced by the simultaneous ingestion of food. Thus, the rate and extent of tacrolimus absorption were greatest under fasted conditions.

In general, it is known that the absorption and bioavailability of a therapeutically active

substance can be affected by a variety of factors when administered orally. Such factors include the presence of food in the gastrointestinal tract and, in general, the gastric residence time of a drug substance is significantly longer in the presence of food than in the fasted state. If the bioavailability of a drug substance is affected beyond a certain point due to the presence of food in the gastrointestinal tract, the drug substance is said to exhibit a food effect. Food effects are important because absorption and hence the plasma levels becomes highly variable depending on food intake. Absorption into the bloodstream may be adversely affected to the point that the patient risks insufficient absorption to remedy the condition for which the drug was administered. On the other hand, the very high peak concentrations seen at fasted conditions occasionally, may very well induce significant side effects, of nephro- or neuro-toxic origin, as well as GI side-effects and others.

Frequently observed side effects are vomiting and nausea but side effects like tremor, headache, hypertension, renal dysfunction, hyperkalemia, hypomagnesaemia, hyperglycemia, insomnia, diarrhea, constipation, abdominal pain, nephrotoxicity and neurotoxicity are also observed.

As mentioned herein before, absorption of tacrolimus from the gastrointestinal tract after oral administration is rapid with a mean time-to –peak concentration (t_{max}) of approximately 1-2 hours after administration to healthy subjects or kidney or liver transplanted patients, but incomplete and variable. The bioavailability is generally as low as at the most about 20% after oral administration.

Tacrolimus is a substrate for both cytochrome P450 IIIA4 (CYP3A4) and P-glycoprotein. Tacrolimus is extensively metabolized by O-demethylation and/or hydroxylation. Eight major metabolites have been proposed. Demethylation and hydroxylation were identified as the primary mechanisms of biotransformation. The major metabolite identified in incubations with human liver microsomes is 13-demethyl tacrolimus. In in vitro studies, a 31-demethyl metabolite has been reported to have the same activity as tacrolimus.

Tacrolimus is extensively metabolized by the CYP3A4 isoenzyme in the gut wall and liver. Therefore, drugs that affect this isoenzyme may influence absorption and the subsequent elimination of systemically absorbed tacrolimus. Inhibitors of CYP3A4 may increase tacrolimus levels, while inducers of CYP3A4 may increase the metabolism of

tacrolimus and decrease tacrolimus levels. Accordingly, tacrolimus may be administered together with one or more CYP3A4 inhibitors in order to improve the overall bioavailability.

Tacrolimus is indicated (or has been suggested) for the treatment of diseases such as, e.g.,

rejection reactions by transplantation of organs or tissues such as the heart, kidney, liver, bone marrow, skin, cornea, lung, pancreas, small intestine, limb, muscle, nerve, intervertebral disc, trachea, myoblast, cartilage, etc.;

graft-versus-host reactions following bone marrow transplantation;

autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, myasthenia gravis, type I diabetes, etc.; and

infections caused by pathogenic microorganisms (e.g. Aspergillus fumigatus, Fusarium oxysporum, Trichophyton asteroides, etc.);

Inflammatory or hyperproliferative skin diseases or cutaneous manifestations of immunologically mediated diseases (e.g. psoriasis, atopic dermatitis, contact dermatitis, eczematoid dermatitis, seborrheic dermatitis, lichen planus, pemphigus, bullous pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, erythema, dermal eosinophilia, lupus erythematosus, acne, and alopecia areata);

autoimmune diseases of the eye (e.g. keratoconjunctivitis, vernal conjunctivitis, uveitis associated with Behcet's disease, keratitis, herpetic keratitis, conical keratitis, corneal epithelial dystrophy, keratoleukoma, ocular premphigus, Mooren's ulcer, scleritis, Graves' ophthalmopathy, Vogt-Koyanagi-Harada syndrome, keratoconjunctivitis sicca (dry eye), phlyctenule, iridocyclitis, sarcoidosis, endocrine ophthalmopathy, etc.);

reversible obstructive airways diseases [asthma (e.g. bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, and dust asthma), particularly chronic or inveterate asthma (e.g. late asthma and airway hyper-responsiveness) bronchitis, etc.];

mucosal or vascular inflammations (e.g. gastric ulcer, ischemic or thrombotic vascular injury, ischemic bowel diseases, enteritis, necrotizing enterocolitis, intestinal damages associated with thermal burns, leukotriene B4-mediated diseases);

intestinal inflammations/allergies (e.g. coeliac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease and ulcerative colitis);

food-related allergic diseases with symptomatic manifestation remote from the gastrointestinal tract (e.g. migrain, rhinitis and eczema);

renal diseases (e.g. intestitial nephritis, Goodpasture's syndrome, hemolytic uremic syndrome, and diabetic nephropathy);

nervous diseases (e.g. multiple myositis, Guillain-Barre syndrome, Meniere's disease, multiple neuritis, solitary neuritis, cerebral infarction, Alzheimer's diseases Parkinson's diseases, amyotrophic lateral sclerosis (ALS) and radiculopathy);

cerebral ischemic disease (e.g., head injury, hemorrhage in brain (e.g., subarachnoid hemorrhage, intracerebral hemorrhage), cerebral thrombosis, cerebral embolism, cardiac arrest, stroke, transient ischemic attack (TIA), hypertensive encephalopathy, cerebral infarction);

endocrine diseases (e.g. hyperthyroidism, and Basedow's disease);

hematic diseases (e.g. pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic anemia, and anerythroplasia);

bone diseases (e.g. osteoporosis);

respiratory diseases (e.g. sarcoidosis, pulmonary fibrosis, and idiopathic interstitial pneumonia);

skin diseases (e.g. dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photosensitivity, and cutaneous T-cell lymphoma);

circulatory diseases (e.g. arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa, and myocardosis);

collagen diseases (e.g. scleroderma, Wegener's granuloma, and Sjogren's syndrome);

adiposis;

eosinophilic fasciitis;

periodontal diseases (e.g. damage to gingiva, periodontium, alveolar bone or substantia ossea dentis);

nephrotic syndrome (e.g. glomerulonephritis);

male pattern alopecia, alopecia senile;

muscular dystrophy;

pyoderma and Sezary syndrome;

chromosome abnormality-associated diseases (e.g. Down's syndrome);

Addison's disease;

active oxygen-mediated diseases [e.g. organ injury (e.g. ischemic circulation disorders of organs (e.g. heart, liver, kidney, digestive tract, etc.) associated with preservation, transplantation, or ischemic diseases (e.g. thrombosis, cardial infarction, etc.));

intestinal diseases (e.g. endotoxin shock, pseudomembranous colitis, and drug- or radiation-induced colitis);

renal diseases (e.g. ischemic acute renal insufficiency, chronic renal failure);

pulmonary diseases (e.g. toxicosis caused by pulmonary oxygen or drugs (e.g. paracort, bleomycin, etc.), lung cancer, and pulmonary emphysema);

ocular diseases (e.g. cataracta, iron-storage disease (siderosis bulbi), retinitis, pigmentosa, senile plaques, vitreous scarring, corneal alkali burn);

dermatitis (e.g. erythema multiforme, linear immunoglobulin A bullous dermatitis, cement dermatitis); and

other diseases (e.g. gingivitis, periodontitis, sepsis, pancreatitis, and diseases caused by environmental pollution (e.g. air pollution), aging, carcinogen, metastasis of carcinoma, and hypobaropathy)];

diseases caused by histamine release or leukotriene C4 release; restenosis of coronary artery following angioplasty and prevention of postsurgical adhesions;

autoimmune diseases and inflammatory conditions (e.g., primary mucosal edema, autoimmune atrophic gastritis, premature menopause, male sterility, juvenile diabetes mellitus, pemphigus vulgaris, pemphigoid, sympathetic ophthalmitis, lens-induced uveitis, idiopathic leukopenia, active chronic hepatitis, idiopathic cirrhosis, discoid lupus erythematosus, autoimmune orchitis, arthritis (e.g. arthritis deformans), or polychondritis);

Human Immunodeficiency Virus (HIV) infection, AIDS;

allergic conjunctivitis;

hypertrophic cicatrix and keloid due to trauma, burn, or surgery.

In addition, the tricyclic macrolides like e.g. tacrolimus have liver regenerating activity and/or activities of stimulating hypertrophy and hyperplasia of hepatocytes. Therefore, the pharmaceutical composition of the present invention is useful for increasing the effect of the therapy and/or prophylaxis of liver diseases [e.g. immunogenic diseases (e.g. chronic autoimmune liver diseases such as autoimmune hepatic diseases, primary biliary cirrhosis or sclerosing cholangitis), partial liver resection, acute liver necrosis (e.g. necrosis caused by toxins, viral hepatitis, shock, or anoxia), hepatitis B, non-A non-B hepatitis, hepatocirrhosis, and hepatic failure (e.g. fulminant hepatitis, late-onset hepatitis and "acute-on-chronic" liver failure (acute liver failure on chronic liver diseases))].

Furthermore, a composition of the present invention is useful for increasing the effect of the prevention and/or treatment of various diseases because of the useful pharmacological activity of the tricyclic macrolides, such as augmenting activity of chemotherapeutic effect, activity of cytomegalovirus infection, anti-inflammatory activity, inhibiting activity against peptidyl-prolyl isomerase or rotamase, antimalarial activity, antitumor activity and so on.

The recommended dosage range for Prograf® is 0.1 to 0.2 mg/kg/day given every 12 hours in two divided doses. More importantly the blood levels has to be monitored. The typical level for 1 – 3 months is 7 –20 ng/mL and 4 – 12 months the levels should be 5 – 15 ng/mL. This is only guiding values and may vary from types of transplant and "race".

The following is for Kidney transplant patients.

	Caucasian n = 114		Black n = 56	
Time After Transplant	Dose (mg/kg)	Trough Concentrations (ng/mL)	Dose (mg/kg)	Trough Concentrations (ng/mL)
Day 7	0.18	12.0	0.23	10.9
Month 1	0.17	12.8	0.26	12.9
Month 6	0.14	11.8	0.24	11.5
Month 12	0.13	10.1	0.19	11.0

The expected dosage recommendation for products of the present invention will be from 0.02 mg/kg/day to 0.15 mg/kg/day, dosed once a day.

The invention is further illustrated in the following examples without limiting it thereto.

Methods

Determination of weight variation

The tablets prepared in the Examples herein were subject to a test for weight variation performed in accordance with Ph. Eur.

Determination of average tablet hardness

The tablets prepared in the Examples herein were subject to at test for tablet hardness employing Schleuniger Model 6D apparatus and performed in accordance with the general instructions for the apparatus.

Determination of disintegration time

The time for a tablet to disintegrate, i.e. to decompose into particles or agglomerates, was determined in accordance with Ph. Eur.

Determination of geometric weight mean diameter d_{gw}

The geometric weight mean diameter was determined by employment of a method of laser diffraction dispersing the particulate material obtained (or the starting material) in air. The measurements were performed at 1 bar dispersive pressure in Sympatec Helos equipment, which records the distribution of the equivalent spherical diameter. This distribution is fitted to a log normal volume-size distribution.

When used herein, "geometric weight mean diameter" means the mean diameter of the log normal volume-size distribution.

Determination of dissolution rate

The dissolution rate was determined by employment of USP paddle dissolution method at 37 °C.

Examples

For the preparation of a pharmaceutical composition in particulate form according to the invention the method described in WO 03/004001 (by the present inventors) has been employed. The method ensures a controlled agglomeration process, i.e. a strict control of the growth in particle size while at the same time it is possible to use a relatively large amount of an oil or an oily-like material.

Examples on Tacrolimus formulation based on controlled agglomeration

HPMC refers to Metolose 90 SH (type 2208) or Metolose 60 SH (type 2910) from ShinEtsu, available in different degree of polymerisation (viscosity, 3-100.000 cP) Either tablets, capsules or granules might be enteric coated with different types of polymers such as hydroxypropylmethylcellulose acetate succinate (Aqoat), cellulose

acetate phthalate CAP, hydroxypropylmethylcellulose phtalate HPMCP or methacrylic acid copolymers such as Eudragit L30D, Eudragit 100/S, Eudragit 100/L

Example 1

Immediate release tablet with improved bioavailability

Substances	%	mg
Tacrolimus	0.50	1.00
Lactose 200 mesh	49.75	100.00
PEG 6000	34.48	69.30
Poloxamer 188	14.78	29.70
Magnesium stearate	0.50	1.01
Total	100.00	201.01

Tacrolimus is dissolved in Polyethylene glycol 6000 and Poloxamer 188 (70:30 w/w ratio) at 70 °C. The solution is sprayed on 250 g lactose in a fluid bed Strea-1. The granular product is sieved through sieve 0.7 mm and blended with magnesium stearate for 0.5 min in a Turbula mixer.

The mixture is compressed into 8 mm tablets with a strength of 1 mg (200 mg tablet with compound cup shaped.
Mean disintegration time: 20 min, Hardness: 45 N

Example 2

Modified release polydepot capsule based on swelling hydrocolloid matrix of hydroxypropylcellulose

Substance	%	mg
Tacrolimus	0.50	1.00
HPMC	20.00	40.00
Lactose 200 mesh	30.00	60.00
PEG 6000	34.65	69.30
Poloxamer 188	14.85	29.70
Total	100.00	200.00

Tacrolimus is dissolved in Polyethylene glycol 6000 and Poloxamer 188 (70:30 w/w ratio) at 70 °C. The solution is sprayed on a mixture of 150 lactose and 100 g HPMC in a fluid bed Strea-1. The granular product is sieved through sieve 0.7 mm and filled into hard gelatine capsules (200 mg)

Example 3

Modified release polydepot capsule based on swelling hydrocolloid matrix of hydroxypropylcellulose

Substance	%	mg
Tacrolimus	0.50	1.00
HPMC 2910 3 cp	20.00	40.00
Lactose 200 mesh	30.00	60.00
Glyceryl monostearate	49.50	99.00
Total	100.00	200.00

Tacrolimus is dissolved in Glycerylmonostearate at 70 °C. The solution is sprayed on a mixture of 150 lactose and 100 g HPMC in a fluid bed Strea-1. The granular product is sieved through sieve 0.7 mm and filled into hard gelatine capsules (200 mg)

Example 4

Modified release matrix tablet based on swelling hydrocolloid matrix of hydroxypropylcellulose

Substance	%	mg
Tacrolimus	0.50	1.00
HPMC	19.90	40.00
Lactose 200 mesh	29.85	60.00
PEG 6000	34.48	69.30
Poloxamer 188	14.78	29.70
Magnesium stearate	0.50	1.01
Total	100.00	201.01

Tacrolimus is dissolved in Polyethylene glycol 6000 and Poloxamer 188 (70:30 w/w ratio) at 70 °C. The solution is sprayed on 250 g lactose in a fluid bed Strea-1. The

granular product is sieved through sieve 0.7 mm and blended with HPMC and magnesium stearate for 0.5 min in a Turbula mixer.

The mixture is compressed into 8 mm tablets with a strength of 1 mg (200 mg tablet with compound cup shaped.
Mean disintegration time: 20 min, Hardness: 45 N

Example 5
Modified release matrix tablet based on lipophilic matrix of glyceryl monostearate

Substance	%	mg
Tacrolimus	0.50	1.00
Lactose 200 mesh	49.75	100.00
Glycerylmonostearate	49.25	99.00
Magnesium stearate	0.50	1.01
	100.00	201.01

Tacrolimus is dissolved in Glyceryl monostearate at 70 °C. The solution is sprayed on 250 g lactose in a fluid bed Strea-1. The granular product is sieved through sieve 0.7 mm and blended with magnesium stearate for 0.5 min in a Turbula mixer.
The mixture is compressed into 8 mm tablets with a strength of 1 mg (200 mg tablet with compound cup shape.
Mean disintegration time: 20 min, Hardness: 45 N

The tablets were subjected to dissolution testing without further coating, as descriped below.

Dissolution profile for Example 5 tablets of Tacrolimus

Time (hours)	% released
0	0
0.5	2
1	4

3	6
8	17
24	37

Example 6

Modified release polydepot capsule based on lipophilic matrix of glyceryl-monostearate

Substance	%	mg
Tacrolimus	0.50	1.00
Lactose 200 mesh	49.75	100.00
Glycerylmonostearate	49.25	99.00
Magnesium stearate	0.50	1.01
	100.00	201.01

Tacrolimus is dissolved in Glyceryl monostearate at 70 °C. The solution is sprayed on 250 g lactose in a fluid bed Strea-1. The granular product is sieved through sieve 0.7 mm and filled into hard gelatine capsules (200 mg).

Example 7

Modified release polydepot Tablet based on lipophilic matrix of gelucire 44/14

Substance	%	mg
Tacrolimus	0.50	1.00
Aeroperl 300	49.75	100.00
Gelucire 44/14	49.25	99.00
Magnesium stearate	0.50	1.01
	100.00	201.01

Tacrolimus is dissolved in gelucire at 70 °C. The solution is sprayed on 250 g aeroperl in a fluid bed Strea-1. The granular product is sieved through sieve 0.7 mm and filled into hard gelatine capsules (200 mg).

The granulate is compressed into 8 mm tablets with strength of 1 mg (tablet weight 200 mg). Tablets are cup shaped.
Mean disintegration time: 25 min, Hardness: 43 N

Capsules and tablets from Examples 1 – 4 and 6-7 were coated with a "delayed" release coating.

The composition of the coating is shown in the table below.

Ingredients	%
Eudragit L30D	40
Purified water	52
Triethyl acethylcitrate	1.8
Antifoam emulsion	0.2
Talcum	6
Total	100

Preparation of coating suspension:
Triethyl acethylcitrate, antifoam emulsion and purified water are mixed by Ultra Turrax at 9500 rpm for 30 min. After 1 min talcum is added. The mixture is strained through sieve 300 and stirred by magnet. Eudragit is strained through sieve 300 and added the mixture. Stirring for 5 min. The coating is stirred throughout the coating process.

The process condition of the coating process is shown in the following table.

Inlet temp, °C	40
Feed rate, g/min	5 (position 14)
Outlet temp, °C	31
Air inlet, m^3/h	140
Nozzle size, mm	0.8
Coating time, min	app. 50 (300g coating)

App. 400 g of tablets, or 200 g of capsules were coated

The film coated tablets and capsules were cured for 48 hours at 30 °C before dissolution testing.

According to US 6,576,259 B2 the dissolution method refers to the Japanese Pharmaceopoeia which is in accordance with USP. The following conditions are outlined:
Paddle speed: 50 rpm.
Dissolution media adjusted to pH = 4.5 (buffer not specified). Phosphate buffer according to Ph.Eur. 4th Ed., 0.05M phosphate buffer solution pH 4.5 (4009000) will be used.
Amount of dissolution media not specified (900 ml standard).
Addition of 0.005% HPMC is specified but not the specific type (Pharmacoat 606 will be used)

The composition of the dissolution media pH=4.5 is shown in the following table:

Ingredients	Amount
Potassium dihydrogen phosphate	6.8 g
HPMC	0.05 mg
Purified water	Ad 1000.0 ml

Tacrolimus was quantified by LCMS.

Dissolution profile for example 2 capsules of tacrolimus

Time (hours)	% Released
00.0	00
01.5	00
02.0	00
04.0	01
06.0	03
08.0	05
10.0	20
15.0	40

Dissolution profile for Example 4 tablets of tacrolimus

Time (hours)	% Released
00.0	00
01.0	00
02.0	00
04.0	03
06.0	04
08.0	07
10.0	14
16.0	38

Claims

1. A solid solution for pharmaceutical use comprising tacrolimus dissolved in a water-miscible solid carrier, wherein the concentration of tacrolimus in the water-miscible carrier is at the most 15% w/w.

2. A solid solution according to claim 1, wherein the concentration of tacrolimus in the water-miscible carrier is at the most 10% w/w such as, e.g., at the most 8% w/w, at the most 6% w/w, at the most 5% w/w, at the most 4%w/w, at the most 3% w/w or at the most 2% w/w.

3. A solid solution according to claim 1, wherein the concentration of tacrolimus in the water-miscible carrier is at least about 0.01% w/w such as, e.g., at least about 0.05% w/w, at least about 0.1% w/w, at least about 0.5% w/w or at least about 1% w/w.

4. A solid solution according to any of the preceding claims, wherein the water-miscible carrier is selected from the group consisting of polyethylene glycols that have a melting point of at least 20 °C, polyoxyethylene oxides, poloxamers, polyoxyethylene stearates, poly-epsilon caprolactone, polyvinylpyrrolidones, polyvinyl-polyvinylacetate copolymer (PVP-PVA), polyvinyl alcohol (PVA), polymethacrylic polymers (Eudragit RS; Eudragit RL, Eudragit NE, Eudragit E), cellulose derivatives including hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), methylcellulose, sodium carboxymethylcellulose, hydroxyethyl cellulose, pectins, cyclodextrins, galactomannan, alginater carragenates, xanthan gums, Gelucire, and the like and mixtures thereof.

5. A solid solution according to any of the preceding claims is admixed with one or more release modifying agents selected from the group consisting of water-miscible polymers, water-insoluble polymers and oils or oily-like materials to obtain a solid mixture.

6. A solid solution according to claim 5, wherein the water-miscible polymer is a cellulose derivative selected from the group consisting of hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), methylcellulose, sodium carboxymethylcellulose, hydroxyethyl cellulose, poloxamers, polyoxyethylene stearates, poly -ε-caprolactone, polyvinylpyrrolidone (PVP), polyvinylpyrrolidone-polyvinylacetate copolymer PVP-PVA (Kollidon VA64), poly-methacrylic polymers

(Eudragit RS, Eudragit RL, Eudragit NE, Eudragit E) and polyvinyl alcohol (PVA), poly(ethylene oxide) (PEO) and the like.

7. A solid solution according to claim 5, wherein the water-miscible polymer is a polymer that has a pH-dependant water-solubility and the polymer is selected from the group consisting of polyacrylamides; phthalate derivatives such as acid phthalates of carbohydrates including amylose acetate phthalate, cellulose acetate phthalate, cellulose acetate terephtahalate, cellulose acetate isophthalate, other cellulose ester phthalates, cellulose ether phthalates, hydroxypropyl cellulose phthalate, hydroxypropylcellulose acetate phthalate, hydroxypropyl ethylcellulose phthalate, hydroxypropyl methylcellulose phthalate (HMPCP), methylcellulose phthalate, methyl cellulose acetate phthalate, polyvinyl acetate phthalate, polyvinyl acetate hydrogen phthalate, sodium cellulose acetate phthalate, starch acid phthalate; phthalates of other compounds including polyvinyl acetate phthalate (PVAP); other cellulose derivatives including hydroxypropyl methylcellulose acetate succinate (HPMCAS), carboxymethylcellulose, cellulose acetate trimellitate; alginates; carbomers; polyacrylic acid derivatives such as acrylic acid and acrylic ester copolymers, polymethacrylic acid and esters thereof, poly acrylic methacrylic acid copolymers, methacrylic acid copolymer (Eudragit L, Eudragit S); styrene-maleic acid dibutyl phthalate copolymer, styrene-maleic acid polyvinylacetate phthalate copolymer, styrene and maleic acid copolymers; shellac, starch glycolate; polacrylin; vinyl acetate and crotonic acid copolymers and the like.

8. A solid solution according to claim 5, wherein the water-insoluble polymer is selected from the group consisting of ethyl cellulose, cellulose acetate, cellulose nitrate, and mixtures thereof.

9. A solid solution according to claim 5, wherein the oil or oily-like material is selected from the group consisting of hydrophilic and hydrophobic oils or oily-like materials.

10. A solid solution according to claim 9, wherein the oil or oily-like material is hydrophilic and selected from the group consisting of: polyether glycols such as, e.g., polypropylene glycols; polyoxyethylenes; polyoxypropylenes; poloxamers, Gelucire 50/13, other Gelucire types such as, e.g., Gelucire 44/14 etc., Gelucire 50/10, Gelucire 62/05 and mixtures thereof.

11. A solid solution according to claim 9, wherein the oil or oily-like material is hydrophobic and selected from the group consisting of: straight chain saturated hydrocarbons, sorbitan esters, paraffins; fats and oils such as e.g., cacao butter, beef tallow, lard, polyether glycol esters; higher fatty acid such as, e.g. stearic acid, myristic acid, palmitic acid, higher alcohols such as, e.g., cetanol, stearyl alcohol, low melting point waxes such as, e.g., glyceryl monostearate, glyceryl monooleate, hydrogenated tallow, myristyl alcohol, stearyl alcohol, substituted and/or unsubstituted monoglycerides, substituted and/or unsubstituted diglycerides, substituted and/or unsubstituted triglycerides, yellow beeswax, white beeswax, carnauba wax, castor wax, japan wax, acetylate monoglycerides; NVP polymers, PVP polymers, acrylic polymers, or a mixture thereof.

12. A solid solution according to claim 11, wherein the oil or oily-like hydrophobic material has a melting point that is about 20 °C or more.

13. A solid solution according to any of claims 5-12, wherein the solid mixture is in powder form.

14. A solid solution according to any claims 5-13 wherein the solid mixture has a geometric weight mean diameter d_{gw} of ≥10 μm such as, e.g. ≥20 μm, from about 20 to about 2000, from about 30 to about 2000, from about 50 to about 2000, from about 60 to about 2000, from about 75 to about 2000 such as, e.g. from about 100 to about 1500 μm, from about 100 to about 1000 μm or from about 100 to about 700 μm, or at the most about 400 μm or at the most 300 μm such as, e.g., from about 50 to about 400 μm such as, e.g., from about 50 to about 350 μm, from about 50 to about 300 μm, from about 50 to about 250 μm or from about 100 to about 300 μm.

15. A pharmaceutical composition comprising a solid solution as defined in any of claims 1-14 together with one or more pharmaceutically acceptable excipients.

16. A pharmaceutical composition according to claim 15, wherein the one or more pharmaceutically acceptable excipients are selected from the group consisting of fillers, disintegrants, binders and lubricants.

17. A pharmaceutical composition according to claim 15 or 16 in powder form.

18. A method for the preparation of a solid solution according to any of claims 1-4, the method comprising dissolving tacrolimus in a water-miscible solid carrier to obtain a solid solution.

19. A method according to claim 18 further comprising a step of applying the solid solution to one or more release modifying agents optionally in admixture with one or more pharmaceutically acceptable excipients.

20. A method according to claim 19, wherein the further step is performed by spraying the solid solution in liquid form on the one or more release modifying agents that optionally are in admixture with one or more pharmaceutically acceptable excipients.

21. Use of a solid solution as defined in any of claims 1-14 for the preparation of an immediate release solid dosage form.

22. Use of a solid solution as defined in any of claims 1-14 for the preparation of a controlled release solid dosage form.

23. Use of a solid solution as defined in any of claims 1-14 for the preparation of a oral dosage form.

24. Use of a solid solution as defined in any of claims 1-14 for the preparation of a topical dosage form.

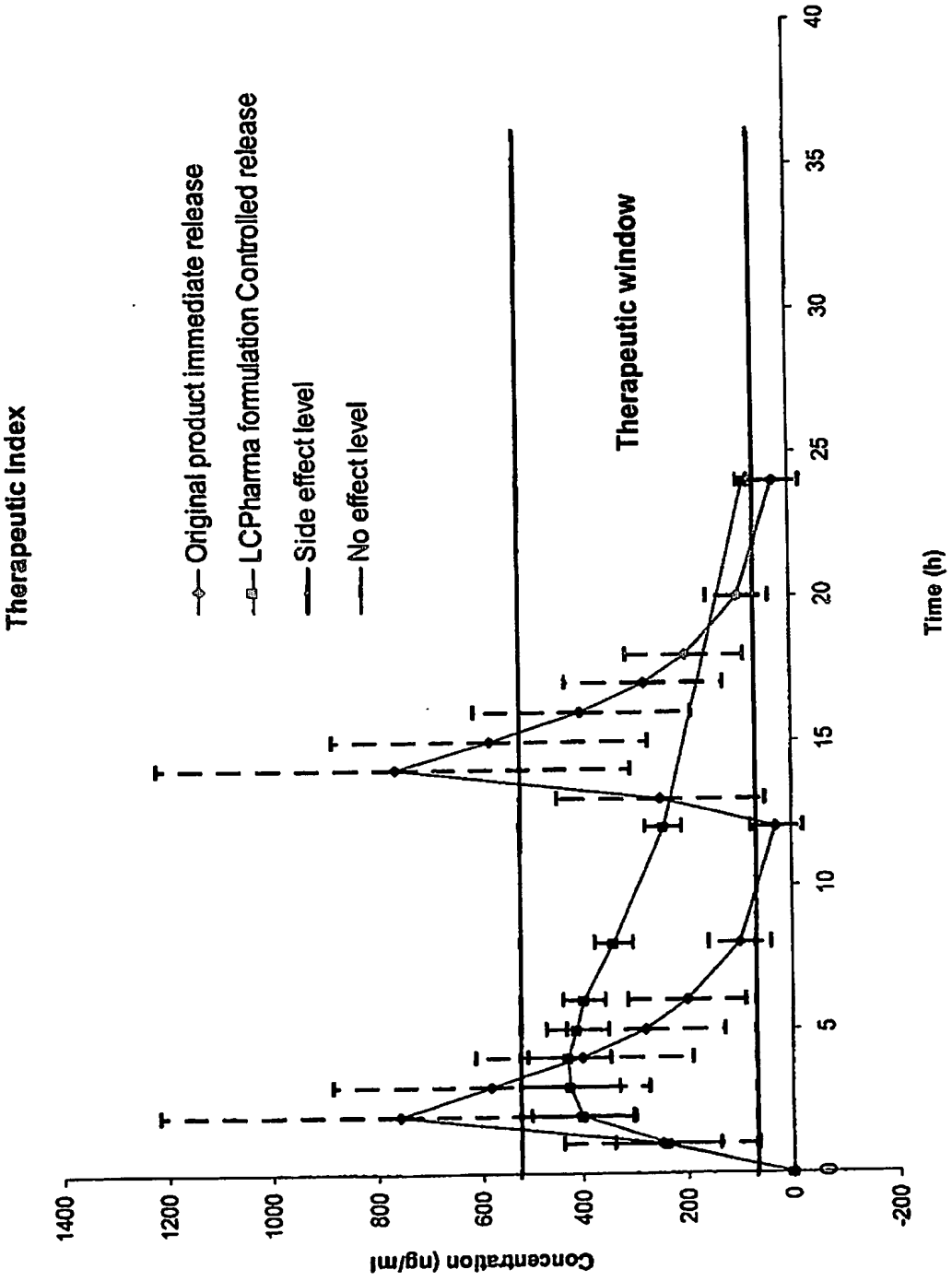


Fig. 1

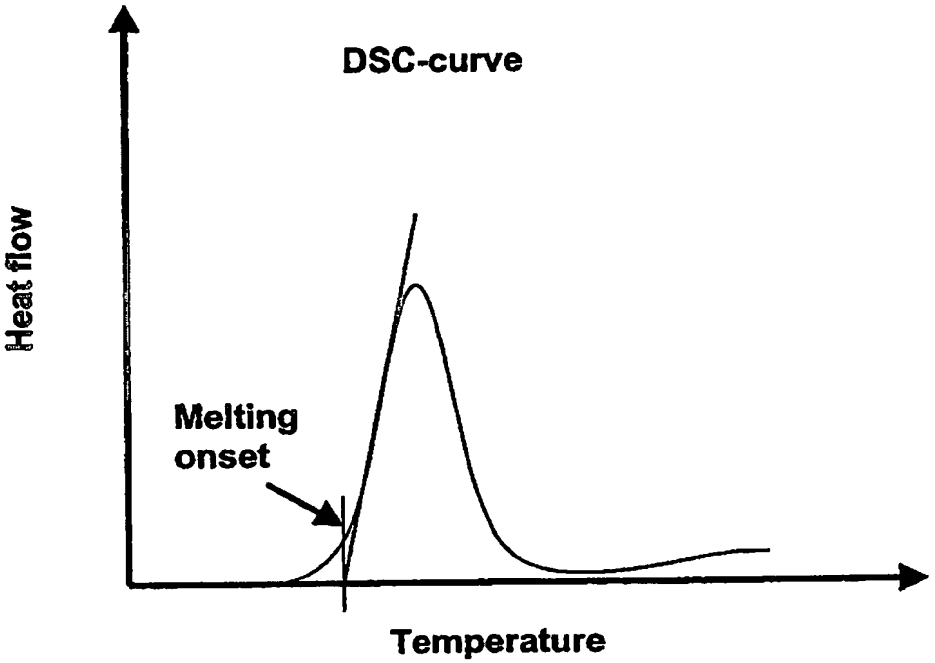


Fig. 2